

CLAIMS

1. Liquid pharmaceutical formulation for the prolonged release of active principle(s) (AP), this formulation comprising an aqueous colloidal suspension of low viscosity based on submicronic particles of water-soluble biodegradable polymer (PO) carrying hydrophobic groups (HG), said particles being non-covalently associated with at least one active principle (AP), characterized in that:
- ◆ the dispersion medium of the suspension consists essentially of water,
 - ◆ said formulation is capable of being injected parenterally and then forming a gelled deposit in vivo, this formation of a gelled deposit:
 - on the one hand being at least partly caused by at least one physiological protein present in vivo,
 - and on the other hand making it possible to prolong and control the in vivo release time of the AP beyond 24 h after administration,
 - ◆ it is liquid under the injection conditions,
 - ◆ and it is also liquid at the physiological temperature and/or at the physiological pH and/or in the presence of:
 - * a physiological electrolyte in a physiological concentration,
 - * and/or at least one surfactant.
2. Formulation according to claim 1, characterized in that its concentration of [PO] is set at a sufficiently high value to allow the formation of a gelled deposit in vivo after parenteral injection, in the presence of at least one physiological protein.
3. Liquid pharmaceutical formulation for the prolonged release of active principle(s) (AP), this formulation:
- being liquid in the ambient atmosphere,
 - also being liquid at the physiological temperature and/or at the physiological pH and/or in the presence of:
 - * a physiological electrolyte in a physiological concentration,
 - * and/or at least one surfactant,
 - and comprising an aqueous colloidal suspension of low viscosity based on submicronic particles of water-soluble biodegradable polymer PO carrying hydrophobic groups HG, said particles being non-covalently associated with at least one active principle AP, and the dispersion medium of the suspension

consisting essentially of water,
characterized in that its concentration of [PO] is set at a sufficiently high value to allow the formation of a gelled deposit in vitro, in the presence of at least one protein.

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4. Formulation according to any one of the preceding claims, characterized in that its concentration of [PO] is such that:

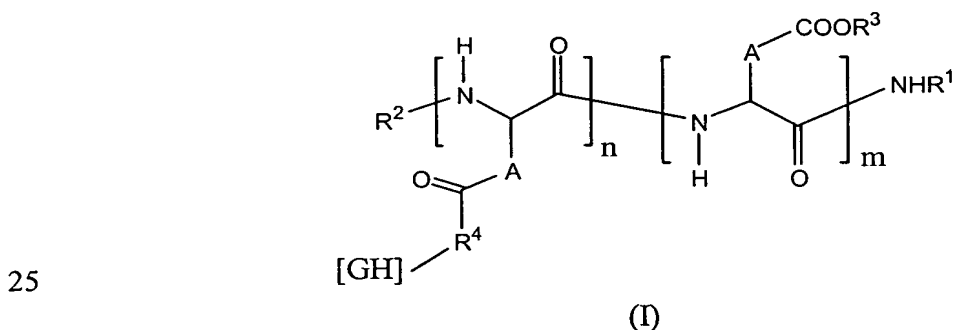
- [PO] \geq 0.9.C1,
- preferably 20.C1 \geq [PO] \geq C1,
- 10 ▪ and particularly preferably 10.C1 \geq [PO] \geq C1,

where C1 is the “*induced gelling*” concentration of the particles of PO, as measured in an IG test.

5. Formulation according to any one of the preceding claims, characterized in
15 that its viscosity is less than or equal to 5 Pa.s.

6. Formulation according to any one of the preceding claims, characterized in that the polymer PO is a polyamino acid formed of aspartic units and/or glutamic units, at least some of these units carrying grafts containing at least one hydro-
20 phobic group (HG).

7. Formulation according to claim 6, characterized in that the PO is (are) defined by general formula (I) below:

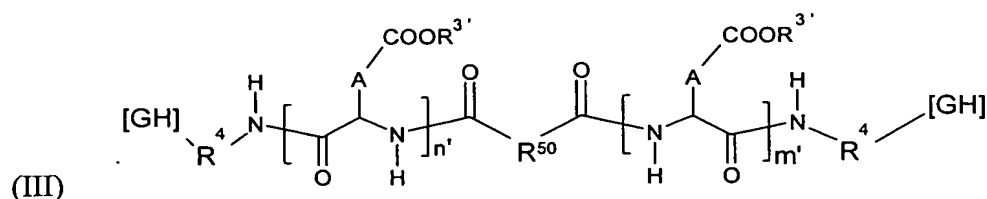
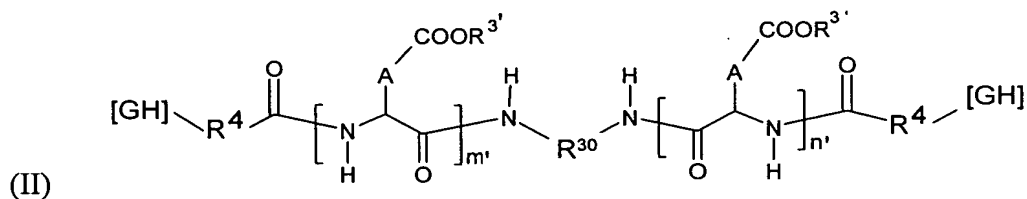


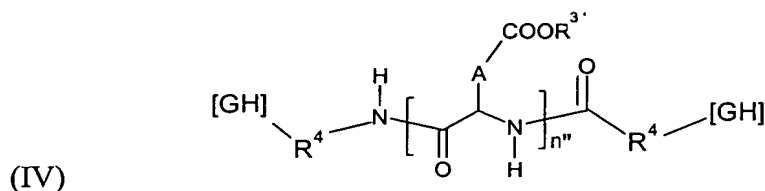
in which:

- R¹ is H, a linear C2 to C10 alkyl or branched C3 to C10 alkyl, benzyl, a
30 terminal amino acid unit or -R⁴-[HG];

- R^2 is H, a linear C2 to C10 acyl or branched C3 to C10 acyl group, a pyroglutamate or $-R^4-[HG]$;
- R^3 is H or a cationic entity preferably selected from the group comprising:
 - metal cations advantageously selected from the subgroup comprising sodium, potassium, calcium and magnesium,
 - organic cations advantageously selected from the subgroup comprising:
 - cations based on amine,
 - cations based on oligoamine,
 - cations based on polyamine (polyethylenimine being particularly preferred),
 - and cations based on amino acid(s) advantageously selected from the class comprising cations based on lysine or arginine,
 - and cationic polyamino acids advantageously selected from the subgroup comprising polylysine and oligolysine;
- R^4 is a direct bond or a "spacer" based on 1 to 4 amino acid units;
- A independently is a radical $-\text{CH}_2-$ (aspartic unit) or $-\text{CH}_2-\text{CH}_2-$ (glutamic unit);
- $n/(n + m)$ is defined as the molar grafting rate and its value is sufficiently low for PO, dissolved in water at pH 7 and at 25°C, to form a colloidal suspension of submicronic particles of PO, $n/(n + m)$ preferably being between 1 and 25 mol% and particularly preferably between 1 and 15 mol%;
- $n + m$ varies from 10 to 1000 and preferably between 50 and 300;
- HG is a hydrophobic group.

8. Formulation according to claim 6, characterized in that the PO has (have) one of general formulae (II), (III) and (IV) below:

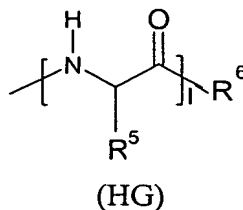




in which:

- HG is a hydrophobic group;
- 5 ▪ R^{30} is a linear C2 to C6 alkyl group;
- $R^{3'}$ is H or a cationic entity preferably selected from the group comprising:
 - metal cations advantageously selected from the subgroup comprising sodium, potassium, calcium and magnesium,
 - organic cations advantageously selected from the subgroup comprising:
 - 10 • cations based on amine,
 - cations based on oligoamine,
 - cations based on polyamine (polyethylenimine being particularly preferred),
 - and cations based on amino acid(s) advantageously selected from the class comprising cations based on lysine or arginine,
 - 15 - and cationic polyamino acids advantageously selected from the subgroup comprising polylysine and oligolysine;
- R^{50} is a C2 to C6 alkyl, dialkoxy or diamine group;
- R^4 is a direct bond or a "spacer" based on 1 to 4 amino acid units;
- 20 ▪ A independently is a radical $-\text{CH}_2-$ (aspartic unit) or $-\text{CH}_2-\text{CH}_2-$ (glutamic unit);
- $n' + m'$ or n'' is defined as the degree of polymerization and varies from 10 to 1000 and preferably between 50 and 300.

9. Formulation according to claim 7 or 8, characterized in that the HG of the
- 25 PO each independently of one another are a monovalent radical of the formula below:



in which:

- R^5 is a methyl (alanine), isopropyl (valine), isobutyl (leucine), sec-butyl (isoleucine) or benzyl (phenylalanine);
 - R^6 is a hydrophobic radical containing from 6 to 30 carbon atoms;
- 5 - l varies from 0 to 6.

10. Formulation according to claim 9, characterized in that all or some of the hydrophobic radicals R^6 of the PO are independently selected from the group of radicals comprising:

- 10 ▪ a linear or branched alkoxy containing from 6 to 30 carbon atoms and optionnally of containing at least one heteroatom (preferably O and/or N and/or S) and/or at least one unit of unsaturation,
- an alkoxy containing 6 to 30 carbon atoms, having one or more fused carbocyclic rings and optionally containing at least one unit of unsaturation
- 15 and/or at least one heteroatom (preferably O and/or N and/or S),
- an alkoxyaryl or an aryloxyalkyl having 7 to 30 carbon atoms and capable of containing at least one unit of unsaturation and/or at least one heteroatom (preferably O and/or N and/or S).

- 20 11. Formulation according to claim 9 or 10, characterized in that the hydrophobic radical R^6 of the graft of the PO is derived from an alcohol precursor selected from the group comprising octanol, dodecanol, tetradecanol, hexadecanol, octadecanol, oleyl alcohol, tocopherol and cholesterol.

- 25 12. Formulation according to claim 6, characterized in that the PO consists of an alpha-L-glutamate or alpha-L-glutamic homopolymer.

13. Formulation according to claim 6, characterized in that the PO consists of an alpha-L-aspartate or alpha-L-aspartic homopolymer.

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14. Formulation according to claim 6, characterized in that the PO consists of an alpha-L-aspartate/alpha-L-glutamate or alpha-L-aspartic/alpha-L-glutamic copolymer.

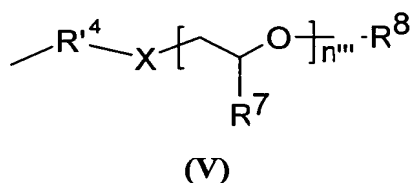
- 35 15. Formulation according to claim 14, characterized in that, in the PO, the

distribution of the aspartic and/or glutamic units carrying grafts containing at least one HG unit is such that the resulting polymer is either random or of the block type or of the multiblock type.

5 16. Formulation according to claim 1, characterized in that the molecular weight of the PO is between 2000 and 100,000 g/mol and preferably between 5000 and 40,000 g/mol.

10 17. Formulation according to claim 6, characterized in that the PO carries at least one graft of the polyalkylene glycol type bonded to a glutamate and/or aspartate unit.

15 18. Formulation according to claim 17, characterized in that the graft of the polyalkylene glycol type has formula (V) below:



in which:

- 20 - R⁴ is a direct bond or a "spacer" based on 1 to 4 amino acid units;
 - X is a heteroatom selected from the group comprising oxygen, nitrogen and sulfur;
 - R⁷ and R⁸ independently are H or a linear C1 to C4 alkyl;
 - n''' varies from 10 to 1000 and preferably from 50 to 300.

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19. Formulation according to claim 17 or 18, characterized in that the polyalkylene glycol is a polyethylene glycol.

30 20. Formulation according to any one of claims 17 to 19, characterized in that the molar percentage of polyalkylene glycol grafting varies from 1 to 30%.

21. Formulation according to any one of claims 1 to 20, characterized in that the hydrophobically modified polymers PO are selected from the group comprising

polyamino acids, polysaccharides (preferably those in the subgroup comprising pullulans and/or chitosans and/or mucopolysaccharides), gelatins and mixtures thereof.

5 22. Formulation according to any one of the preceding claims, characterized in that the AP is a protein, a glycoprotein, a protein bonded to one or more polyalkylene glycol chains [preferably polyethylene glycol (PEG) chains: "PEGylated protein"], a polysaccharide, a liposaccharide, an oligonucleotide, a polynucleotide or a peptide, said AP preferably being selected from haemoglobins,
10 cytochromes, albumins, interferons, cytokines, antigens, antibodies, erythropoietin, insulin, growth hormones, factors VIII and IX, interleukins or mixtures thereof, and haemopoiesis stimulating factors.

23. Formulation according to any one of claims 1 to 21, characterized in that
15 the active principle is a "small" hydrophobic, hydrophilic or amphiphilic organic molecule.

24. Formulation according to any one of claims 1 to 22, characterized in that its weight fraction of AP not associated with the submicronic particles [non-associated
20 AP], in weight %, is such that:

- [non-associated AP] ≤ 1 ,
- preferably [non-associated AP] ≤ 0.5 .

25. Formulation according to any one of the preceding claims, characterized in that it is injectable by the parenteral, subcutaneous, intramuscular, intradermal, intraperitoneal or intracerebral route or into a tumour.

26. Formulation according to any one of the preceding claims, characterized in that it is intended for the preparation of drugs, particularly for administration by the
30 parenteral, subcutaneous, intramuscular, intradermal, intraperitoneal or intracerebral route or into a tumour, or by the oral, nasal, vaginal or ocular route.

27. Process for the preparation of drugs, particularly for administration by the parenteral, subcutaneous, intramuscular, intradermal, intraperitoneal or
35 intracerebral route or into a tumour, or by the oral, nasal, vaginal or ocular route,

characterized in that it consists essentially in using at least one formulation according to any one of claims 1 to 26.

28. Derived product, characterized in that it comprises submicronic particles
5 formed of non-covalent PO/AP associations as defined in claim 1, and in that it is obtained from the formulation according to any one of claims 1 to 26.

29. Derived product according to claim 28, characterized in that it consists of a
10 powder or a gel.

30. Process for the preparation of the formulation according to any one of
claims 1 to 26, characterized in that it consists essentially in:

- ◆ taking a colloidal suspension of nanoparticles of at least one PO,
- ◆ mixing this colloidal suspension of nanoparticles of PO with at least one AP,
15 preferably in aqueous solution,
- ◆ optionally adding at least one excipient,
- ◆ adjusting the pH and/or the osmolality if necessary, and
- ◆ optionally filtering the resulting suspension.

20 31. Process according to claim 30, characterized in that the AP is (are) in the form of an aqueous suspension or solution for mixing with the colloidal suspension of nanoparticles of PO.

25 32. Process for the preparation of the formulation according to any one of claims 1 to 26, characterized in that it consists essentially in:

- ◆ taking a powder of nanoparticles of at least one PO,
- ◆ mixing this powder with an aqueous suspension or solution of at least one AP,
preferably in aqueous solution,
- ◆ optionally adding at least one excipient,
- 30 ◆ adjusting the pH and/or the osmolality if necessary, and
- ◆ optionally filtering the resulting suspension.

33. Process for the preparation of the formulation according to any one of
claims 1 to 26, characterized in that it consists essentially in:

- 35 ◆ taking a powder produced by drying the liquid formulation according to

according to any one of claims 1 to 26,

- ◆ mixing this powder with an aqueous liquid medium, preferably with stirring,
 - ◆ optionally adding at least one excipient,
 - ◆ adjusting the pH and/or the osmolarity if necessary, and
- 5 ◆ optionally filtering the resulting suspension.

34. Process for the preparation of a powder derived from the formulation according to any one of claims 1 to 26, characterized in that said powder is obtained by drying the formulation according to any one of claims 1 to 26.